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SUPPLEMENT ARTICLE

WILEY CLINICAL ORAL IMPLANTS RESEARCH

The use of platelet-rich fibrin to enhance the outcomes of implant therapy: A systematic review

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Abstract

Objective: To assess the impact of platelet-rich fibrin (PRF) on implant dentistry. The primary focused question was as follows: What are the clinical, histological, and radiographic outcomes of PRF administration for bone regeneration and implant therapy?

Method: A systematic literature search comprised three databases: MEDLINE, EMBASE, and Cochrane followed by a hand search of relevant scientific journals. Human studies using PRF for bone regeneration and implant therapy were considered and articles published up to December 31, 2017 were included. Eligible studies were selected based on the inclusion criteria. Randomized controlled trials (RCT) and controlled clinical trials (CCT) were included.

Results: In total, 5,963 titles were identified with the search terms and by hand search. A total of 12 randomized controlled trials (RCT) met the inclusion criteria and were chosen for data extraction. Included studies focused on alveolar ridge preservation after tooth extraction, osseointegration process, soft tissue management, bone augmentation, bone regeneration after sinus floor elevation and surgical peri-implantitis treatment. Overall, the risk of bias was moderate or unclear. Nine studies showed superior outcomes for PRF for any of the evaluated variables, such as ridge dimension, bone regeneration, osseointegration process, soft tissue healing. Three studies failed to show any beneficial effects of PRF. No meta-analysis could be performed due to the heterogeneity of study designs.

Conclusions: There is moderate evidence supporting the clinical benefit of PRF on ridge preservation and in the early phase of osseointegration. It remains unclear whether PRF can reduce pain and improve soft tissue healing. More research support is necessary to comment on the role of PRF to improve other implant therapy outcomes.

KEYWORDS

alveolar ridge preservation, guided bone regeneration, implant therapy, platelet-rich fibrin, sinus floor elevation

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1 | INTRODUCTION

Reduced bone height and width are the most common limitations for implant placement. To overcome these limitations, guided bone regeneration, alveolar ridge preservation, and sinus floor elevation were introduced. Even though most of these techniques provide predictable outcomes, there is a demand to enhance wound healing and bone regeneration either after dental extraction or during implant placement. The local application of growth factors and scaffolds are supposed to enhance wound healing and bone regeneration. The therapeutic concept is based on the assumption that if physiologic concentrations of growth factors are good, a supraphysiological concentration of growth factors even better supports the early stages of wound healing and bone regeneration. However, only few recombinant growth factors are clinically approved by the US regulatory agencies (Nevins et al., 2013; Triplett et al., 2009). Autologous preparation of growth factors from blood usually needs no formal approval. It is nevertheless necessary to critically evaluate the safety and efficacy of the various preparations of platelets and the respective fibrin-rich matrix.

Platelet-rich fibrin (PRF) is prepared from plasma after centrifugation of whole blood (Choukroun, Adda, Schoeffler & Varvelle, 2001). Plasma containing platelets and leukocytes undergo spontaneous coagulation. Like in the natural blood clot that forms at the defect site, activated platelets and leukocytes are entrapped in the fibrin-rich matrix (Singer & Clark, 1999). PRF can be further processed, for example, by squeezing out further serum resulting in a PRF membrane (Dohan et al., 2006) or by mixing with grafts and biomaterials as summarized in this and other reviews.

Systematic reviews recently summarized the effects of PRF related to implant dentistry. Miron et al. focused on intrabony and furcation defects, extraction sockets, sinus lifting, gingival recessions, and bone augmentation (Miron, Zucchelli, et al., 2017) as well as on soft tissue regeneration, augmentation, and/or wound healing (Miron, Fujioka-Kobayashi, et al., 2017). At the same time, Castro et al. provided systematic reviews on alveolar ridge preservation, sinus floor elevation and implant therapy (Castro et al., 2017b) as well as intrabony defects, furcation defects, and periodontal plastic surgery (Castro et al., 2017a). Also, systematic reviews on mandibular third molar extractions (Al-Hamed, Tawfik, Abdelfadil, & Al-Saleh, 2017; Canellas, Ritto, & Medeiros, 2017) and gingival recessions (Moraschini & Barboza Edos, 2016) became available. This study is complementary to these current systematic reviews.

2 | MATERIAL AND METHODS

2.1 | Protocol development and eligibility criteria

This review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) statement, conforming to which a detailed protocol was established (Liberati et al., 2009; Moher et al., 2015). The systematic review was conducted as the second assessing platelet concentrates and implant therapy.

The focused question was formulated based on the PRISMA guidelines:

1. Population (P) = humans with lack of alveolar bone and/or need of implant therapy or tooth extraction.
2. Intervention (I) = use of PRF alone or in combination with a graft material in guided bone regeneration techniques and implant therapy.
3. Comparison (C) = respective surgical procedure without PRF.
4. Outcome (O) = alveolar bone regeneration, soft tissue healing, osseointegration, implant stability, graft resorption, periodontal probing depth and postoperative life quality issues such as pain.
5. Study design (S) = randomized controlled clinical trials, prospective controlled clinical trials, split-mouth or parallel arms.

The following PICOS question was raised: *Is there any additional benefit of PRF on guided bone regeneration and implant therapy over traditional approaches in terms of clinical, histological and radiographic outcomes?*

2.2 | Search strategy

An electronic search of three databases (MEDLINE, EMBASE, CENTRAL) was performed. Articles published up to December 31, 2017 were considered. No language or time restrictions were applied in the search. However, only studies written in English were included for selection. An additional hand search was carried out including the bibliographies of the selected papers and other narrative and systematic reviews as well as in the following journals: *Clinical Oral Implants Research*, *Clinical Implant Dentistry and Related Research*, *European Journal of Oral Implantology*, *Implant Dentistry*, *International Journal of Oral and Maxillofacial Implants*, *International Journal of Periodontics and Restorative Dentistry*, *Journal of Clinical Periodontology*, *Journal of Dental Research*, *Clinical Oral Investigations*, *Journal of Oral and Maxillofacial Surgery*, *Journal of Periodontology*, *Oral Surgery*, and *Oral Medicine*, *Oral Radiology*, *Oral Pathology and Endodontics*.

2.3 | Search terms

The electronic search strategy included terms related to the intervention and used the following combination of key words, MeSH and Emtree terms: “osseointegration” OR “dental Implants, single-tooth” OR “dental implants” OR “tooth implant” OR “guided bone regeneration” OR “bone regeneration” OR “alveolar ridge augmentation” OR “alveolar bone loss” OR “bone resorption” OR “tooth extraction” OR “socket preservation” OR “alveolar process” OR “alveolar ridge preservation” OR “sinus floor augmentation” OR “sinus lifting” OR “sinus

lift" OR "maxillary sinus" AND "platelet-rich fibrin" OR "autologous platelet concentrate" OR "thrombocyte rich plasma" OR "leukocyte platelet-rich fibrin" OR "pure platelet-rich fibrin" OR "LPRF" OR "L-PRF" OR "advanced platelet-rich fibrin" OR "APRF" OR "A-PRF" OR "L-PRF Gel". Cochrane search filters for RCTs and CCTs were implemented, with cohort trials also included. The results were limited to human studies.

2.4 | Inclusion criteria

1. Randomized clinical trials (RCT) or controlled clinical trials (CCT) including at least 10 patients/sites per group.
2. Studies regarding alveolar ridge preservation, soft tissue healing, bone augmentation procedures, or implant therapy combined with platelet-rich fibrin.

2.5 | Exclusion criteria

In vitro and preclinical studies, cohort studies, case series, case reports, retrospective studies, RCTs or CCTs with less than 10 patients/sites per group, and studies not meeting all inclusion criteria.

2.6 | Screening and selection of studies

Publication records and titles identified by the electronic search and hand search were independently screened by two reviewers (FJS and AS) based on the inclusion criteria. Discrepancies were solved by discussion including a third reviewer (RG). Cohen's Kappa-coefficient was used as a measure of agreement between the readers. Thereafter, full texts of the selected abstracts were obtained. Where full texts could not be obtained authors and editors of the respective journal were contacted. The two reviewers independently performed the screening process, that is, from the MeSH/Emtree term search up to the full-text examination. Then, articles that met the inclusion criteria were processed for data extraction.

2.7 | Data extraction and quality assessment

The inclusion criteria were applied for data extraction. The studies were classified according to study design and type of intervention. Then, outcomes were compiled in tables. All extracted data were double-checked, and any questions that came up during the screening and the data extraction were discussed within the authors to aim for consensus. Two reviewers (FJS and AS) independently evaluated the methodological quality of all included studies using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Higgins et al., 2011). All included studies were checked for the following criteria: (a) sequence generation, (b) allocation concealment, (c) blinding of participants and personnel, (d) blinding of outcome assessment, (e) incomplete outcome data, (f) selective reporting, and (g) other bias. Any disagreement was discussed until consensus was achieved. Each study was classified into the following groups: low risk of bias if all quality criteria were judged as "present," moderate risk of bias if one or more key domains were "unclear," and high risk of bias if one or more key domains were not "present."

3 | RESULTS

3.1 | Selection of studies

The literature search identified 5,787 potential references in Medline and 175 in Embase, of which 37 were eligible after title and abstract screening (inter-reviewer agreement κ=0.95 ± 0.03). Hand search identified one more study (Gülsen & Sentürk, 2017). Of the 38 full-text articles, 18 did not meet the inclusion criteria and were excluded (Figure 1; Table 1 of excluded studies). The remaining 18 RCTs and 2 CCTs were discussed in the EAO consensus meeting. Studies dealing with third molar extractions were excluded (Table 1). In consequence, 12 RCTs were included for data extraction. The included studies were divided into subgroups, depending on the area of PRF application (Tables 2–5):

3.2 | Alveolar bone regeneration (Table 2)

1. Alveolar ridge preservation (Table 2*a*): *n* = 3, (Alzahrani, Murriky, & Shafik, 2017; Marenzi, Riccitiello, Tia, di Lauro, & Sammartino, 2015; Temmerman et al., 2016).
2. PRF combined with bone substitutes (Table 2*b*): *n* = 1, (Thakkar, Deshpande, Dave, & Narayankar, 2016).

3.3 | Implant placement (Table 3)

1. Osseointegration process (Table 3a): *n* = 3, (Boora, Rathee, & Bhoria, 2015; Öncü & Alaaddinoglu, 2015; Tabrizi, Arabion, & Karagah, 2017).
2. Soft tissue management (Table 3b): *n* = 1, (Hehn, Schwenk, Striegel, & Schlee, 2016).
3. Horizontal bone augmentation (Table 3c): *n* = 1, (Angelo, Marcel, Andreas, & Izabela, 2015).

3.4 | Sinus floor elevation (Table 4)

Sinus floor elevation (Table 4): *n* = 2, (Nizam, Eren, Akcali, & Donos, 2018; Tatullo et al., 2012).

3.5 | Peri-implantitis defects (Table 5)

Peri-implantitis defects (Table 5): *n* = 1, (Hamzacebi, Oduncuoglu, & Alaaddinoglu, 2015).

3.6 | Exclusion of studies

Exclusion of studies (Table 1) occurred due to insufficient study cohort, missing control group, inappropriate PRF preparation, and application during third molar extraction.

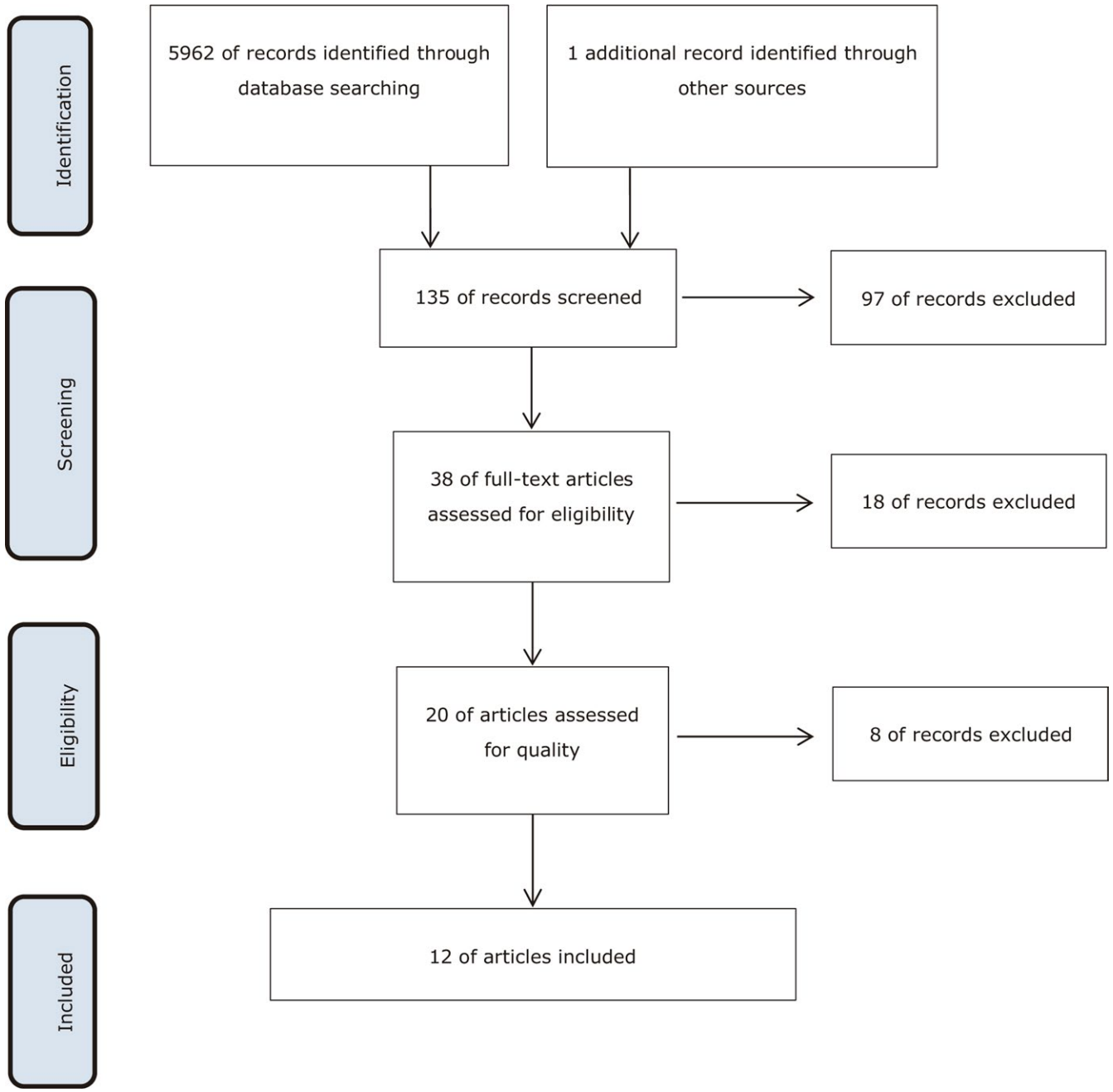

FIGURE 1 PRISMA flow diagram

3.7 | Quality assessment of the included studies

Quality and risk assessment was independently conducted by two authors (FJS and AS) and are represented in Figures 2 and 3. Discrepancies were solved by discussion until reaching consensus. Included RCTs were rated following the Cochrane collaboration's tool for assessing risk of bias. No single study demonstrated low risk of bias for all the criteria and the majority of studies showed a moderate and unclear risk of bias. Most of them provided a detailed report about randomization but not regarding other key domains such as allocation concealment and blinding of the participants, thereby increasing the potential risk of bias. Seven studies described the randomization process and five the allocation concealment in sufficient detail. Two of the studies were registered to an online database, which allows for judgment of selective outcome bias (Öncü & Alaaddinoglu, 2015; Tabrizi et al., 2017). No study described an adequate blinding of patients and personnel. Blinding of outcome assessors was stated in two trials. Three studies described a sample size calculation (Alzahrani et al., 2017; Nizam et al., 2018; Temmerman et al., 2016).

TABLE 1 List of excluded full-text papers and reasons for exclusion following full-text screening

Author and year	Reasons for exclusion
Afat et al. (2017)	Third molars
Agarwal et al. (2015)	Intrabony defects
Baslarli et al. (2015)	Third molars
Bolukbasi et al. (2013)	No control group
Choukroun et al. (2006)	Insufficient number of patients
Cömert-Kilic et al. (2017)	Insufficient number of patients
Das et al. (2016)	PRF being not the only variable
Du Toit et al. (2016)	Insufficient number of patients
Dutta et al. (2016)	Not appropriate PRF protocol
Gürbüzer et al. (2010)	Third molars
Gülsen et al. (2017)	Third molars
Hauser et al. (2013)	Insufficient number of patients
Huang et al. (2016)	Case report
Khan et al. (2017)	PRF protocol
Kumar et al. (2014)	Third molars
Mazor et al. (2009)	No control group
Moussa et al. (2016)	Insufficient number of patients
Ozgul et al. (2015)	Third molars
Shah et al. (2017)	Case report
Singh et al. (2012)	Third molars
Taschieri et al. (2011)	No control group
Toffler et al. (2010)	No control group
Varghese et al. (2017)	Third molars
Yelamali et al. (2015)	No control group
Zhang et al. (2012)	Insufficient number of patients
Zhao et al. (2015)	No control group

3.8 | Study design and evaluation period

A total of four studies were RCTs where a split-mouth design was applied (Marenzi et al., 2015; Nizam et al., 2018; Tabrizi et al., 2017; Temmerman et al., 2016). The remaining RCTs used a parallel group design. The follow-up period ranged considerably from 3 weeks to 12 months.

3.9 | Subject characteristics

All studies included healthy subjects with no active inflammatory disease. The mean age varied from 18 to 79. The number of included patients lied between 10 and 82. Smokers were included in two, excluded in six and not reported in four studies.

3.10 | Data extraction

Included studies presented a high heterogeneity in regards to outcome measures, PRF preparation or study duration. Therefore, a meta-analysis was not feasible.

3.11 | Alveolar ridge preservation (totally 72 patients) (Table 2a)

Two RCTs examined the clinical benefits of PRF in ridge preservation, both with positive adjunctive effects. PRF increased radiographic bone fill at 1, 4, and 8 weeks after tooth extraction and reduced alveolar ridge resorption at 4 and 8 weeks (Alzahrani et al., 2017). Similar findings were reported by Temmerman et al. (2016); PRF helped to preserve horizontal and vertical ridge dimensions 3 months after tooth extraction. Also, postoperative pain was reduced at day 3 and day 5 (Temmerman et al., 2016). Another study found pain relief also within the first 3 days and improved soft tissue healing (Marenzi et al., 2015).

3.12 | Alveolar ridge preservation combined with bone substitutes (totally 36 sites) (Table 2b)

One study looked at the combination of PRF with DFDBA and a collagen membrane showing that alveolar ridge height was preserved to a higher extent (Thakkar et al., 2016).

3.13 | Implant placement: osseointegration process (totally 60 patients) (Table 3a)

The included studies examined the impact of PRF on the initial osseointegration process all showing an enhanced healing. PRF reduced marginal bone loss (Boora et al., 2015). Furthermore, ISQ values were increased after 1 and 4 weeks in the PRF group (Öncü & Alaaddinoglu, 2015) and after 2, 4, and 6 weeks in the posterior maxilla (Tabrizi et al., 2017). Clinical parameters such as probing depth and bleeding on probing as well as implant survival did not change upon PRF treatment compared to control (Boora et al., 2015).

3.14 | Implant placement: soft tissue management (totally 31 patients) (Table 3b)

Soft tissue augmentation with PRF showed an increased peri-implant tissue loss compared to control (Hehn et al., 2016) that was attributed to the slightly different flap design in the test group.

3.15 | Implant placement: horizontal bone augmentation (totally 82 patients) (Table 3c)

PRF was unable to influence the insertion torque when PRF was combined with β-TCP (Angelo et al., 2015).

3.16 | Sinus floor elevation (totally 73 patients) (Table 4)

PRF increased the amount of medullary spaces and osteoid borders (Tatullo et al., 2012). PRF showed no beneficial effects on neither new bone formation, bone height gain, soft tissue, and resorption of

TABLE 2a Included studies: alveolar ridge preservation

Study (year), funding	Study design, duration	No. of patients (implants)	Mean age ± *SD* and/or range	Surgical procedure, no. of L-PRF membrane/clot	Groups T: test C: control (Smokers included)	PRF preparation	Outcome
Alzahrani et al. (2017) NR	RCT 2 months	24	37.8 ± NR 25–50	Tooth extraction without flap elevation w/wo PRF L-PRF membrane: 2 L-PRF clot: NR	T: PRF *n* = 12 C: no PRF *n* = 12 (No)	3,000 rpm/10 min Hardware: [a]	Mean difference of alveolar ridge width (%): SS less resorption in PRF group at 4 (T: 5.2 ± 0.8 vs C: 9.7 ± 6.0, $p = 0.012$) and 8 weeks (T: 8.5 ± 1.7 vs C: 13.5 ± 6.5, $p = 0.036$) post extraction. NS at 1 week (T: 2.0 ± 0.8 vs C: 3.2 ± 2.2, $p = 0.141$) Radiographic bone fill of the extraction socket (%): Better in the PRF group at 1 (T: 74 ± 1.6 vs C: 68.8 ± 1.0, $p = 0.012$), 4 (T: 81.5 ± 3.3 vs C: 74 ± 1.1, $p < 0.05$) and 8 weeks (T: 88.8 ± 1.5 vs C: 80.3 ± 2.6, $p = 0.01$)
Marenzi et al. (2015) NR	RCT split-mouth 3 weeks	26	53 ± 4 NR	Bilateral tooth extraction w/wo L-PRF L-PRF membrane: 0 L-PRF clot: 2–6	T: L-PRF *n* = 26 C: no L-PRF *n* = 26 (Yes)	2,700 rpm/12 min Hardware: [b]	Pain: SS lower in L-PRF group (T: 3.2 ± 0.3 vs C: 4.1 ± 0.1. $p < 0.0001$) Soft tissue healing (healing index): NS at 3 days post-op (T: 4.8 ± 0.6 vs C: 5.1 ± 0.9, $p = 0.197$), SS lower at 7 (T: 4.5 ± 0.5 vs C: 4.9 ± 0.3, $p = 0.05$), 14 (T: 4.2 ± 0.2 vs C: 4.3 ± 0.3, $p = 0.01$) and 21 days (T: 4.1 ± 0.1 vs C: 4.2 ± 0.2, $p = 0.0002$)
Temmerman et al. (2016) NR	RCT split-mouth 3 months	22	54 ± 11 NR	Socket preservation w/wo L-PRF L-PRF membrane: 2–3 L-PRF clot: 2–5	T: L-PRF *n* = 22 C: no L-PRF *n* = 22 (No)	2,700 rpm/12 min Hardware: [b]	Vertical resorption (mm): NS at the lingual aspect (T: −0.4 ± 1.1 vs C: −0.7 ± 0.8, $p > 0.05$), SS less in PRF group at the buccal aspect (T: −0.5 ± 2.3 vs C: −1.5 ± 1.3, $p = 0.0002$) Horizontal resorption (mm); horizontal ridge width at 1, 3 and 5 mm from the crest: • Buccal: at 3 months SS less at 1 mm (T: −0.8 ± 2.5 vs C: −2.9 ± 2.7, $p = 0.003$) and 3 mm (T: −0.4 ± 1.5 vs C: −1.0 ± 1.1, $p = 0.04$) from the crest and NS at 5 mm from the crest (T: −0.4 ± 1.7 vs C: −0.5 ± 0.6, $p = 0.38$) • Lingual: at 3 months SS less at 1 mm (T: −0.6 ± 2.2 vs C: −2.1 ± 2.5, $p = 0.004$). NS at 3 mm (T: −0.1 ± 0.3 vs C: −0.3 ± 0.3, $p = 0.06$) and 5 mm (T: −0.0 ± 0.1 vs C: −0.1 ± 0.0, $p = 0.06$) from the crest Total width reduction (%): SS less at 1 mm (T: −22.8 ± 24.2 vs C: −51.9 ± 40.3, $p = 0.0004$), 3 mm (T: −5.4 ± 6.1 vs C: −14.5 ± 19.6, $p = 0.007$) and 5 mm (T: −2.9 ± 4.5 vs C: −4.4 ± 4.8, $p = 0.02$) from the crest Socket fill (%): SS better in PRF group (T: 94.7 ± 26.9 vs C: 63.3 ± 31.9, $p = 0.004$) Postoperative pain: SS less pain at day 3, 4 and 5 in the L-PRF group ($p < 0.005$)

Note. RCT, randomized controlled clinical trial; CCT, controlled clinical trial; *SD*, standard deviation; NR, not reported; w/wo, with or without; wo, without; SS, statistical significant difference; NS, no statistical difference; [a], Compact centrifuge, Hermle labortechnik, Germany; [b], Intra-SpinTM L-PRF kit, Intra-Lock, Boca-Raton, FL, USA.

TABLE 2b Included studies: alveolar ridge preservation combined with bone substitutes

Study (year), funding	Study design, duration	No. of patients (implants)	Mean age ± *SD* and/or range	Surgical procedure, no. of L-PRF membrane/clot	Groups T: test C: control (Smokers included)	PRF preparation	Outcome
Thakkar et al. (2016) NR	RCT 6 months	NR	NR 20–55	Socket preservation + DFDBA + CM w/wo PRF L-PRF membrane: 1 L-PRF clot: 0	T: DFDBA + PRF *n* = 18 sites C: DFDBA wo PRF *n* = 18 sites (No)	3,000 rpm/10 min Hardware: NR	Difference of ridge width: SS less difference in width from baseline to 180 days in the PRF group (T: 0.75 ± 0.49 vs C: 1.36 ± 0.70; $p = 0.005$) Difference of ridge height: NS (T: −1.08 ± 0.42 vs C: −1.38 ± 0.50, $p = 0.058$)

Note. RCT, randomized controlled clinical trial; CCT, controlled clinical trial; *SD*, standard deviation; NR, not reported; w/wo, with or without; wo, without; SS, statistical significant difference; NS, no statistical difference; DFDBA, demineralized freeze-dried bone allograft; CM, collagen membrane.

DBBM (Nizam et al., 2018) nor on the implant survival at 12 (Nizam et al., 2018) and 36-month follow-up (Tatullo et al., 2012).

3.17 | Peri-implantitis defects (totally 19 patients) (Table 5)

One study assessed the clinical outcome of open flap debridement with and without PRF. PRF increased the probing depth reduction, increased the gain in clinical attachment and reduced mucosal recession after 3 and 6 months (Hamzacebi et al., 2015).

4 | DISCUSSION

The present systematic review focused on RCTs using PRF in all fields of implant dentistry including alveolar ridge preservation and/or augmentation, implant placement, sinus floor augmentation, and peri-implantitis. The aim was to evaluate the current literature with respect to the clinical indications for PRF in bone regeneration and in soft tissue healing in respect to implant therapy. The selected publications revealed a great heterogeneity with a general lack of conclusive evidence, in large part due to low power and incomplete reporting of the study design. Owing to the heterogeneity of the studies no meta-analysis could be performed.

4.1 | Alveolar bone regeneration

The main goal of alveolar ridge preservation is to preserve the hard and soft tissue following tooth extraction and to facilitate implant placement in a prosthetically driven position. Two studies evaluated the dimensional changes of the alveolar process using L-PRF only (Alzahrani et al., 2017; Temmerman et al., 2016). Both studies concluded that PRF reduces alveolar width resorption from 8 weeks to up to 6 months postoperatively. Both studies used more than one L-PRF clot or membrane: Alzahrani et al. inserted 2 membranes and Temmerman et al. inserted 3–7 membranes. The number of clots or membranes within a site and the respective blood volume might affect the clinical outcome (Castro et al., 2017b). In consequence, the number of membranes/clots might modulate the cellular microenvironment in the socket.

One study assessed ridge preservation using the combination of L-PRF with demineralized freeze-dried bone allografts (DFDBA) (Thakkar et al., 2016). In the PRF group, the ridge width demonstrated fewer dimensional changes over 180 days. However, Thakkar et al. cannot be compared with the aforementioned studies as here a grafting material was used. Moreover, they utilized only one clot compared to the multiple clots/membranes used by others (Alzahrani et al., 2017; Marenzi et al., 2015; Temmerman et al., 2016). Marenzi et al. reported an improvement in soft tissue healing after 7, 14, and 21 days; however, the clinical interpretation is challenging due to the plethora of healing indexes in the literature. Moreover, based on a single study it is difficult to draw a strong conclusion. Another relevant aspect that requires further

TABLE 3a Included studies: implant placement, osseo-integration process

Study (year), funding	Study design, duration	No. of patients (implants)	Mean age ± *SD* and/or range	Surgical procedure, no. of L-PRF membrane/clot	Groups T: test C: control (Smokers included)	PRF preparation	Outcome
Boora et al. (2015) NR	RCT 3 months	20 (20)	24.6 ± NR 18–33	One-stage, non-functional immediate implant w/wo PRF L-PRF membrane: 1	T: Implant + L-PRF *n* = 10 C: Implant wo L-PRF *n* = 10 (NR)	3,000 rpm/10–12 min Hardware:[g]	Bone level changes: SS less initial marginal bone loss for L-PRF group at mesial and distal site at 1 and 3 months • Mesial: at 1st (T: 0.1 ± 0.0 vs C: 0.3 ± 0.1, $p = 0.007$) and 3rd month (T: 0.2 ± 0.0 vs C: 0.5 ± 0.2, $p = 0.0004$) • Distal: at 1st (T: 0.1 ± 0.0 vs C: 0.3 ± 0.1, $p = 0.02$) and 3rd month (T: 0.2 ± 0.0 vs C: 0.6 ± 0.2, $p = 0.0006$) PPD (mm): NS at all time points • Mesial: at 1st (T: 5 ± 0.8 vs C: 5.3 ± 0.6, $p > 0.05$) and 3rd month (T: 3.0 ± 1.1 vs C: 3.1 ± 0.3, $p > 0.05$) • Distal: at 1st (T: 5.1 ± 0.7 vs C: 5.1 ± 0.8, $p > 0.05$) and 3rd month (T: 3.6 ± 0.8 vs C: 3.8 ± 0.7, $p > 0.05$) Bleeding on probing (%): NS at 1st (T: 50 vs C: 50, $p > 0.05$) and 3rd month (T: 20 vs C: 30, $p > 0.05$) Survival rate (%): 100 in both groups
Öncü et al. (2015) NR	RCT 1 month	20 (64)	44.2 ± 12.5 (NR)	Implants coated w/wo PRF L-PRF membrane: 1 + L-PRF exudate	T: 31 implants + PRF C: 33 implants w/o PRF (Yes)	2,700 rpm/12 min Hardware:[h]	ISQ: SS higher ISQ values after 1 (T: 69.2 ± 10.5 vs C: 60.0 ± 12.2, $p = 0.002$) and 4 weeks (T: 77.1 ± 6.0 vs 70.4 ± 7.7, $p = 0.001$)
Tabrizi et al. (2017) Institutional	RCT split-mouth 6 weeks	20 (40)	39.6 ± 6.74 (NR)	Bilateral implant placement w/wo PRF L-PRF membrane: 1	T: PRF *n* = 20 C: no PRF = 20 (NR)	2,800 rpm/10 min Hardware:[b]	ISQ: SS higher in the PRF group at 2 (T: 60.6 ± 3.4 vs C: 58.2 ± 3.6, $p = 0.04$), 4 (T: 70.3 ± 3.3 vs C: 67.1 ± 4.3, $p = 0.014$) and 6 weeks (T: 78.5 ± 3.3 vs C: 76.1 ± 2.9, $p = 0.027$)

Note. RCT, randomized controlled clinical trial; CCT, controlled clinical trial; *SD*, standard deviation; NR, not reported; w/wo, with or without; SS, statistical significant difference; NS, no statistical difference; ISQ, Implant stability quotient; PPD, periodontal pocket depth. [g], centrifuge model R-8C, Remi, India; [h], PC-02, Process Ltd; [b], Intra-SpinTM L-PRF kit, Intra-Lock, Boca-Raton, FL, USA.

TABLE 3b Included studies: implant placement, soft tissue management

Study (year), funding	Study design, duration	No. of patients (implants)	Mean age ± *SD* and/or range	Surgical procedure, no. of L-PRF membrane/clot	Groups T: test C: control (Smokers included)	PRF preparation	Outcome
Hehn et al. (2016) Self-funded	RCT 6 months	31 (31)	53.8 ± NR 33–79	Implant placement w/ wo soft tissue augmentation with L-PRF L-PRF membrane: 1 L-PRF clot: 0	T: Implant + L-PRF *n* = 10 C: Implant no L-PRF *n* = 21 (No)	NR Hardware:[b]	Mucosa thickness changes between baseline and 3 months (mm): • At the crest: SS thickness loss in the PRF group (T: 2.2 ± 0.4 to 0.9 ± 1, $p < 0.05$), NS thickness loss in the control group (C: 2.6 ± 0.4 to 2.6 ± 0.6, $p > 0.05$) • Buccal: NS changes in both groups (T: 1.8 ± 0.4 to 2.1 ± 0.7, $p > 0.05$; C: 2.2 ± 0.4 to 2.3 ± 0.4, $p > 0.05$) • Lingual: NS changes in both groups (T: 1.5 ± 0.4 to 1.8 ± 0.6, $p > 0.05$; C: 1.6 ± 0.5 to 1.8 ± 0.5, $p > 0.05$) Bone loss (defect depth/defect width) (mm): NS in PRF group (T: 0.7 ± 0.4/0.5 ± 0.4 mesial, T: 0.8 ± 0.4/0.6 ± 0.3 distal vs C: 0.7 ± 0.6/0.5 ± 0.4 mesial, C: 0.8 ± 0.7/0.5 ± 0.5 distal, $p > 0.05$)

Note. RCT, randomized controlled clinical trial; *SD*, standard deviation; NR, not reported; w/wo, with or without; SS, statistical significant difference; NS, no statistical difference; [b], Intra-SpinTM L-PRF kit, Intra-Lock, Boca- Raton, FL, USA.

TABLE 3c Included studies: implant placement, horizontal bone augmentation

Study (year), funding	Study design, duration	No. of patients (implants)	Mean age ± *SD* and/or range	Surgical procedure, no. of L-PRF membrane/clot	Groups T: test C: control (Smokers included)	PRF preparation	Outcome
Angelo et al. (2015) NR	RCT 8 months	82 (109)	NR 29–71	Piezotome enhanced subperi-osteal tunnel technique in the anterior maxilla a-PRF membrane: NR a-PRF clot: NR	T1: 60% HA/40% β-TCP + PLGA layer *n* = NR(36) T2: β-beta-TCP + PLGA layer *n* = NR(35) T3: β-beta-TCP + PLGA layer + aPRF exu-date + aPRF *n* = NR (38) C: no bone graft *n* = 26(30) (NR)	NR Hardware: NR	Insertion-torque-values (Ncm): NS between T3 and T2 (T3: 46.8 ± 4.5 vs T2: 42.5 ± 7, $p > 0.05$)

Note. RCT, randomized controlled clinical trial; *SD*, standard deviation; NR, not reported; w/wo, with or without; SS, statistical significant difference; NS, no statistical difference; ISQ, Implant stability quotient; β-TCP, tricalcium phosphate; HA, hydroxyapatite; PLGA, polylactic-co-glycolic acid; a-PRF, advanced platelet-rich fibrin.

TABLE 4 Included studies: sinus floor elevation

Study (year), funding	Study design, duration	No. of patients (implants)	Mean age ± *SD* and/or range	Surgical procedure, no. of L-PRF membrane/clot	Groups T: test C: control (Smokers included)	PRF preparation	Outcome
Nizam et al. (2017) NR	RCT split-mouth 12 months	13 (26)	49.9 ± 10.3 35–67	SFE + DBBM w/wo L-PRF L-PRF membrane: 1–2 mixed w/ DBBM	T: DBBM + L-PRF *n* = 13 C: DBBM wo L-PRF *n* = 13 (No)	400 *g*/12 min Hardware: [a]	Histological analysis: NS qualitative differences Histomorphometry: • Newly formed bone (BV/TV%): NS (T: 21.3 ± 8.7 vs C: 21.2 ± 5.5, *p* = 0.96) • Residual bone graft (BSV/TV%): NS (T: 25.9 ± 9.5 vs C: 32.7 ± 5.8, *p* = 0.6) • Bone graft in contact with new bone (%): NS (T: 47.3 ± 12.3 vs C: 54.0 ± 8.3, *p* = 0.16) • Soft tissue (%): NS (T: 52.6 ± 12.5% vs C: 45.9 ± 8.3%, *p* = 0.16) Radiographic augmented bone height (mm): NS (T: 13.6 ± 1.0 vs C: 13.5 ± 1.2, *p* = 0.88) Implant survival rate: 100% in both groups at 12 months after implant loading
Tatullo et al. (2012) NR	RCT 5 months	60	NR 43–62	SFE + DBBM w/wo PRF followed by implant placement L-PRF membrane: 2 L-PRF clot: 2	T: PRF *n* = 36 sites C: no PRF *n* = 24 sites (No)	3,000 rpm/10 min Hardware: NR	Histomorphometry: • Medullary spaces (%): Higher values in PRF group, *p* = NR • Osteoid borders (%): Higher values in PRF group, *p* = NR • Trabecular bone (%): Lower values in PRF group, *p* = NR Survival rate: 100% in both groups at 36 ± 10 months

Note. RCT, randomized controlled clinical trial; CCT, controlled clinical trial; *SD*, standard deviation; NR, not reported; SFE, sinus floor elevation; w/wo, with or without; wo, without; SS, statistical significant difference; NS, no statistical difference; DBBM, deproteinized bovine bone mineral (Bio-Oss®); β-TCP, tricalcium phosphate; [a], Nüve Laboratory Equipments, NF200, Ankara, Turkey.

TABLE 5 Included studies: peri-implantitis

Study (year), funding	Study design, duration	No. of patients (implants)	Mean age ± *SD* and/or range	Surgical procedure, no. of L-PRF membrane/clot	Groups T: test C: control (Smokers included)	PRF preparation	Outcome
Hamzacebi et al. (2015) Institutional	RCT 6 months	19 (38)	60.9 ± 11.9 48–73	Surgical treatment of peri-implantitis: OFD w/wo L-PRF L-PRF membrane: NR L-PRF clot: NR	T: OFD + L-PRF n = 19 C: OFD n = 19 (NR)	3,000 rpm/10 min Hardware: NR	PD (mm): SS lower mean values at 6 months in PRF group (T: 3.3 ± 0.4 vs C: 3.7 ± 0.4, p < 0.001). SS higher PD reduction in L-PRF group (T: 2.8 ± 1.0 vs C: 2.0 ± 0.7, p = 0.001) CAL (mm): SS more CAL gain in L-PRF group at 3 months (T: 2.8 ± 1.0 mm vs C: 1.4 ± 1.0, p < 0.01) and maintained at 6 months (T: 3.3 ± 1.0 vs C: 1.8 ± 0.8, p < 0.01) Mucosal recession (mm): SS less recession after treatment in L-PRF group at 3 (T: 0.1 ± 0.2 vs C: 1.0 ± 0.6 p < 0.001) and 6 months (T: 0.1 ± 0.2 vs C: 1.0 ± 0.6, p < 0.001) Survival rate: 100% at 6 months follow-up in both groups

Note. RCT, randomized controlled clinical trial; *SD*, standard deviation; NR, not reported; w/wo, with or without; SS, statistical significant difference; NS, no statistical difference; OFD, open flap debridement; PPD, periodontal pocket depth; CAL, clinical attachment level.

FIGURE 2 Quality assessment of the included studies: Risk of bias summary

attention is the regenerative potential of L-PRF on different biotypes that is not reported in either of the studies. There is also a general lack of patient characteristics that can influence bone resorption.

4.2 | Implant placement

Five studies were included with respect to PRF application during implant placement. Two RCTs assessed the impact of PRF prior to implant insertion (Öncü & Alaaddinoglu, 2015; Tabrizi et al., 2017). Higher ISQ values were detected in the test group compared to noncoated implants. This implies that PRF might enhance implant stability during the early phase of osseointegration. Another study showed less marginal bone loss with PRF (Boora et al., 2015). However, this data is limited to implants with a follow-up of 3 months. Furthermore, no effects on bone loss were observed when a PRF membrane was placed over the implant (Hehn et al., 2016). There was even a decrease in mucosa thickness after 3 months in the PRF group, and the study was terminated after 10 cases (Hehn et al., 2016). Overall, due to the heterogeneity of the

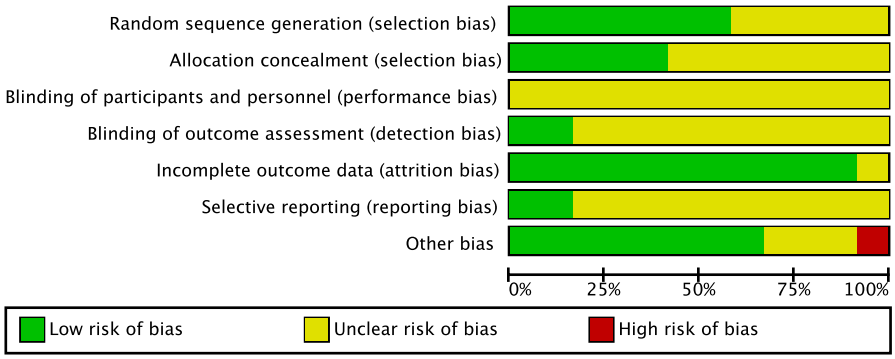

FIGURE 3 Quality assessment of the included studies: Risk of bias graph

outcome measures, it is difficult to draw a conclusion from PRF during implant placement. This is also true for implant placement combined with horizontal bone augmentation (Angelo et al., 2015) where PRF failed to affect insertion torque.

4.3 | Sinus floor elevation

Sinus floor elevation procedures are highly effective yet not free of complications. Complications associated with sinus floor elevation include graft resorption, membrane perforation, or sinusitis. Two studies met the inclusion criteria (Nizam et al., 2018; Tatullo et al., 2012). Implant survival rate was 100% after a one (Nizam et al., 2018) and 3-year (Tatullo et al., 2012) follow-up, regardless of PRF. These two studies combined PRF with DBBM. No RCT could be identified where PRF was used as the sole filling material or in combination with autologous bone. In addition, PRF did not change bone formation, soft tissue area, resorption of residual bone grafts, and the augmented bone height (Nizam et al., 2018). The studies did not report on membrane perforations and sinusitis, precluding any conclusion about its potential benefit in the management of complications. Although in vitro and preclinical data (Miron, Zucchelli, et al., 2017) encourage the use of PRF in sinus floor elevation, the clinical evidence gathered so far does not support its use. Moreover, neither of the two studies assessed patient-reported outcomes.

In summary, inconclusive results are reported on PRF in sinus floor elevation procedures whereby a lack of well-designed studies with appropriate endpoints are needed. Therefore, the effect of PRF on bone regeneration during sinus floor elevation remains questionable.

4.4 | PRF and pain

Pain is a relevant patient-reported outcome measure (Coulthard, Patel, Bailey, & Coulthard, 2014). Two studies reported patient-reported outcomes measured using the visual analog scale (Marenzi et al., 2015; Temmerman et al., 2016). Temmerman et al. (2016) concluded that PRF significantly reduced pain sensations after 3 to 5 days and Marenzi et al. (2015) noted significantly less pain in the PRF group up to the 21st day. Nevertheless, it has to be taken into account that both studies did not state whether the patients were adequately blinded. There are numerous studies assessing PRF effect on pain with mandibular third molar extraction (Al-Hamed et al., 2017). However, only few studies used a blinded protocol (Afat, Akdogan, & Gonul, 2017; Ozgul et al., 2015). In consequence, patient-reported outcomes such as pain must be interpreted with caution.

4.5 | Peri-implantitis

Peri-implantitis requires new approaches and techniques to be established. One approach might be the use of PRF. Only one RCT, with a 6-month follow-up, observed the effect of PRF in peri-implantitis defects (Hamzacebi et al., 2015). Although a significant improvement of pocket reduction, clinical attachment gain, and mucosal recession was found in the PRF group, it is not possible to draw a definitive conclusion. The defects were insufficiently described in their anatomy. Whether PRF is effective in peri-implantitis defects remains to be investigated with further well-designed RCTs.

5 | CONCLUSION

Based on studies with a rather limited statistical power, the present systematic review suggests that (i) PRF might reduce alveolar width resorption, and might enhance implant stability during the early phase of osseointegration. (ii) PRF combined with grafting materials has no effect in sinus floor elevation, and, (iii) there is a lack of adequate studies for implant placement, peri-implantitis defects, soft tissue healing, and postoperative pain, although the preliminary data seems promising.

6 | FUTURE DIRECTION

The studies included in this review mainly focused on surrogate parameters to evaluate the effect of PRF. The clinical relevance of the outcome measurements remains questionable. Even though it is possible to use PRF in almost every procedure in implant dentistry, its potential clinical benefit on the long-term outcomes has not yet been established. A low number of studies report on

implant placement and peri-implantitis. With regards to sinus floor elevation, RCTs investigating PRF as the sole filling material or in combination with autologous bone need to be carried out. Another interesting aspect that requires further attention is to investigate possible effects of PRF in medically compromised patients or in extraction sockets with severe buccal bone deficiency. It needs to be evaluated in which clinical situations and for what patient group PRF is most effective. In addition, the number of PRF membranes to obtain a clinical benefit still remains unclear. Further well-designed RCTs are necessary to state, in which clinical indication and for what kind of patients the use of PRF can be recommended.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

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